Recruitment for Clinical Trials – A Challenge for Electronic Support?

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Research

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Abstract

Introduction One of the most challenging and most meaningful designs in medical research are clinical trials (CTs). One essential step before a CT can start is recruitment, i. e., to identify patients that fit to the study design and which fulfill the inclusion and do not fulfill the exclusion criteria. The recruitment for CTs might be supported by means of modern information technologies. The aims of the present work were 1) to evaluate which tools (not necessarily electronical) are actually used in clinical routine and 2) to evaluate in which way and of which kind electronic support would be helpful for the clinical staff. Methods Semi-standardized interviews were performed in five wards (cardiology, gynaecology, gastroenterology, nephrology, and palliative care) in a German university hospital. The interviewees were all directly involved in patient recruitment. Three of them were clinicians, one was a study nurse, and one was a research assistant. Results All interviewees reported that either feasibility estimations as well as recruitment is mostly done from memory, although there would be many possibilities where IT support could assist. However, all participants reported some kind of IT support. Searches in ward-specific patient registers (data bases) and searches in Clinical Information Systems were reported. Furthermore, free text searches in medical reports were mentioned. There was no preference whether active or passive systems would be desired for potentially future applications. However, unless IT support, the most relevant factor for successful recruitment that was mentioned by all of the interviewees was personal motivation. Conclusions Overall, IT support has a minor standing in the recruitment for CTs today. The lack of IT usage and the estimations from memory that were reported from all of the participants, might bind cognitive resources which might district from clinical routine. We conclude that the recruitment for CT is still a challenge for electronic support and that education of the clinic staff about the possibilities is compellingly necessary.

1 Background

One of the most challenging and most meaningful designs in medical research are clinical trials (CTs). Many instructions how to design a CT optimally can be found in the literature (e.g., [1] [2]). However, the probably most challenging and essential steps before a clinical trial can start are the phases of feasibility and recruitment (i.e., the identification of patients that fit to the study design). This is hampered by inclusion and exclusion criteria (IC, EC) which must be fulfilled. The recruitment for CTs might be supported by means of modern information technologies (ITs) and hospitals and other research organizations are challenged to establish appropriate IT architectures [3]. The aims of the present work were, first, to evaluate by means of semi-standardized interviews which tools (not necessarily electronical) are actually used in clinical routine in different sections in a German hospital and, second, to evaluate in which way and of which kind electronic support would be helpful for the clinical staff.

1.2 Difficulties as Regards Patient Recruitment

It is a frequently published and, therefore, well-known fact that patient recruitment is a crucial factor for the success of a CT and that failing to achieve recruitment objectives is a common problem [4] [5]. This

problem can be traced from 1984 [6] until very recently [7] [8] without seeing a significant change. A lot of research has been spent for unveiling and discussing typical problems as regards achieving planned recruitment goals [9]. Several reviews analyzed strategies to improve recruitment accrual [10] [11] [12], but found that the specific solutions from individual trials are not easily generalizable [5].

One major problem is staff workload and lack of time as regards the patient recruitment [4] [13] Therefore, electronic support might accelerate the recruitment procedure and, therefore, relieve the staff. On further problem is that often the staff has not access to and awareness of relevant trial information, which is often available on paper documents only [4] [14]. Further problems are that often clearly defined, unambigious eligibility IC and EC [4], are missing. Inclusion and EC are often written manually, making the mapping to electonically available data difficult [4] [14]. Therefore, one point on which electronic support might start is the balancing of eligibility criteria, so that on one hand the required number of participants can be recruited, but that on the other hand the target population fits as well as possible with the goal of the study [4] [15].

1.3 Electronic Support Strategies

Clinical Information Systems (CIS), Electronic Health Records (EHRs) and – more generally – Health Information Systems (HIS) are often considered a suitable tool for supporting the process of clinical trial management [4] [9] [16]. In general, there are three strategies how patient identification and patient recruiting for clinical trials can be supported by means of HIS [16]:

systems that restrospectively query existing data in a HIS (Clinical Trial Recruitment Support Systems),

systems that monitor the occurence of a specific event in a HIS in order to create some kind of alert (Clinical Trial Alert Systems), and

systems that require an operator to enter appropriate data to trigger an eligibility assessment.

These are usually specialized subtypes or component modules of Clinical Decision Support Systems (CDSS). Their purpose is to automatically generate patient lists or pro-active alerts which need to be noticed and dealt with by the respective target audience [4]. Several approaches and solutions have been presented in the last years [16]. Alerts can be sent out using paging systems [17] [18], mobile devices [19] or e-mails [20] [21] [22] or can be sent directly within the HIS/CDSS [13] [23] [24] or with a combination of these methods [25] [26].

One of the key challenges as regards the design and operation of an active system is to find an operational mode that has the least possible influence on the usual workflow of the target audience [16]. In addition, the threshold must be balanced carefully between a sensitivity that produces a high number of eligible patients and a specifity that avoids alert fatigue [4] [17] [23] [24].

1.4 Recruitment Workflow

While many articles regarding the support of clinical trials by means of secondary use data have been published, most of them present prototypes or stand-alone solutions (e.g., [17], [18], [19]). Many authors agree that the impact on the routine workflow of the involved staff needs to be kept as low as possible and that understanding these workflows is crucial [4] [16] [27]. However, little research has been spent on these routine workflows outside the setting of the site-specifc solutions. Furthermore, only few articles dwell on the involved actors or roles. A precise description was published by Embi et al. [23] [24] and includes the involved physicians, main investigators and clinical research assistants. Another analysis of the trial managment workflow of oncological phase III and phase IV trials at two sites in São Paulo and Rio de Janeiro was carried out by de Carvalho et. al. [28]. They found a lack of standardized processes for data capture, a multiplicity of data repositories and a shortage of decision support systems. They concluded that workflows are needed to be reorganized by using information technology more efficiently and that standard procedures are needed to be established.

Moreover, a strong focus on the role of physicians and the medical disipline of oncology can be observed in previous research [29]. Although the role of the physicians is very important [23], they are not the only party involved on the bedside. Nurses and dedicated trial personnel also need to be considered.

1.5 Motivation and Aims

To summarize, the identification and recruitment of patients for clinical trials is a well-known and still existing problem. Information technology-based solutions must fit into the respective workflows [16] [27], but these workflows have been remained largely without investigation.

Our goal was to conduct an investigation and an analysis of clinical workflows to find out when, where and how IT can and should provide supporting tools. We focused on the real-world implementation of workflows, regardless of theoretical or pre-defined models as described in [14]. To achieve these goals, we performed semi-standardized interviews in a German university hospital.

Keeping in mind that trial management is a complex process and likely to require individual approaches fitted to the respective setting, we aimed to include 1) a variety of medical disciplines and 2) a variety of medical staff. As regards 2), we only considered personnel that is directly involved in identifying and recruiting patients for clinical trials, with a strong focus towards the bedside staff, since the latter is the usually burdened with non-trial related duty and, therefore, most likely hampered by suboptimal workflows.

2 Methods

2.1 Participants

Interviews were performed with five participants (2 male, mean age = 37.2 ± 7.9 years) from different wards (cardiology, gynaecology, gastroenterology, nephrology, and palliative care) of a German university hospital. All of the participants were directly involved in patient recruitment. Three were physicians, one

was a research assistant, and one a study nurse. Written and informed consent was provided by all of the participants. The study was approved by the local ethics committee of the Friedrich-Alexander University Erlangen-Nuremberg.

2.2 Data collection and analysis

Semi-standardized interviews were performed with the participants. Each interview lasted about 30 minutes. Interviews were voice-recorded electronically and were transcribed and anonymized before analysis. Furthermore, a short questionnaire which assesses demographic variables was filled out by the participants.

Interviews were divided into four parts: first, the actual study feasibility assessment, second, the actual patient recruitment, third, the actual IT support, and fourth, the request for IT support. The whole interview guidelines can be found in Appendix 1.

The interview data was analyzed by two independent raters (AN and LB) with respect to the four interview parts (1) study feasibility – actual state,2) patient recruitment – actual state, 3) IT support – actual state, 4) IT support – request).

3 Results

3.1 Study feasibility – actual state

At first, the actual state of study feasibility estimations was estimated, i.e. the assessment of whether there are enough patients available which fulfill the inclusion, but not the EC. All interviewees reported that most of the feasibility estimation is done from memory and is mostly based on experience. They reported that in mind, a comparison with previous studies is performed which in most cases offers good results for similar studies, but which works rather badly for new types of investigations. One interviewee named the screening of paper-based medical records by the study nurses for non-interventional studies. Most of the participants reported an active exchange between study nurses and clinicians for assessing feasibility estimations irrespective of the responsibilities, i.e. the study nurses reported that they ask the clinicians and vice versa. However, regular team meetings were reported by three of the five interviewees only. In two of these meetings, IC and EC were exchanged between the involved parties.

One clinician and the research assistant reported extrapolation from previous years' data based on specific databases. However, they mentioned that some therapy situations have not been documented (well). The research assistant also reported doing an extensive literature search for getting prevalence rates and extrapolating this for the patient numbers in the actual clinic. Only one (the research assistant) reported an ongoing documentation of feasibility estimations. Furthermore, the study nurse reported creating screening list with screened patients and reason for exclusion for some studies.

All interviewees stated that they never receive feedback how good their estimations were, making it impossible to improve over time. Overall, the actual state of study feasibility estimation was dominated

by human communication and estimations in mind. IT support had nearly no importance so far.

3.2 Patient recruitment – actual state

The interviewees named different strategies for patient recruitment. Most of them named announcement in local newspapers and postings in local offices. This was especially done when an external sponsor was involved. However, only a tiny fraction of the participants comes by themselves in respondence to newspaper announcements.

The most important strategy was asking the stationary patients during regular ward rounds or during patient contact in the outpatient clinic, i.e. most of the recruitment is done in the outpatient clinic or the inpatient clinic, respectively. Four of the interviewees reported that all clinicians – not only specialized study doctors or nurses – are involved in the recruitment. The operational steps (for the clinicians) are as follows: the clinician contacts the study nurses who select possible patients from memory, from data bases or from (paper-based) records. After this, the doctors contact the patients. This does not obstruct the routine, because most steps are done in mind. For known patients, the patient's attitude to the specific type of study is considered in advance. On the other side, the research assistant reported no division of labor and that there is one dedicated employee per study, responsible for the entire workflow. He reported that an alert from clinical personnel does not work well.

Three of the interviewees reported that they search actively in a CIS. One reported searching in paper-based patient records or in Word documents (when data is not in CIS and because free text search is not possible in CIS). The applied strategy depends on the study. One clinician reported that he uses a study book some studies which is kept up-to-date by the clinicians and to which the study nurses have access to. One clinician mentioned paper-based reminder notes with the IC and EC which can be found in the treatment rooms. Another recruitment way that was mentioned by the study nurse is that the clinician asks the team whether there is an eligible study for a specific patient. Two of the clinicians reported that, for most of the studies, the clinicians know all IC and EC.

Again, it was reported that regular team meetings and regional conferences take place in which it is decided which patients are eligible for inclusion.

The research assistant and the study nurse reported a written documentation of patient recruitment strategy and reason for inclusion or exclusion, respectively. The others stated that screening protocols would definitively be helpful but are not suitable because of time pressure.

One interviewee stated that the burden for patient recruitment depends on the study: Stationary patients with high care expense are good to recruit, but recruitment in clinical routine is often forgotten.

Most of the interviewees stated that the most relevant factor for successful recruitment is the personal motivation and not the specific tools that are used for this. Overall, the actual state of the recruitment procedure was also dominated by human communication and estimations from memory. Electronic support is used but has less importance so far.

3.3 IT support – actual state

Although much is actually done from memory, all participants reported some kind of IT support.

One clinician reported to have a ward-specific patient register for specific diagnoses with comprehensive entries (e.g., blood samples) which has been especially built for CT recruitment. He stated that this database is very extensive, because the head physician is a recognized expert in his field. Furthermore, he mentioned that it is possible to use medical reports in principle but that there are too many patients to screen all of them. Therefore, most is done in mind anyways, i.e. every passing patient is screened in mind during the clinical routine. He also stated that hard numbers (e.g., blood samples) make little sense in his case because operational reports are of more importance. He also noted that he searches only sparsely in the clinical information system. He mentioned that there is a lot of data in free-text medical reports but that it is time consuming to scan all of it. A further problem is that the specific diagnosis is not documented in some of these reports. Moreover, it is not documented whether the patient already participates in another study.

The study nurse reported that she always searches in the CIS for blood samples for example. Furthermore, she performs free text searches in Word documents and emphasizes that this needs further interpretation from her side.

Another clinician reported that he does not search in the CIS at all. He searches in Excel lists (data bases) for specific diseases or working groups instead. Furthermore, he used an electronic data capture (EDC) systems for one study, but this is not permitted for other studies because of data protection policies.

Another clinician reported that proposals for patients are recorded in the Electronic Data Processing by the nurses. The study nurses get an alert before the clinician contacts the patient and can remind him to recruit the patient. Furthermore, he mentioned a specific study database which is a central register. Moreover, specifically study-relevant data is documented in the CIS which is specifically used for the regional conferences. However, not enough data is being collected electronically. Furthermore, this clinician reported that they use their own database for documenting recruitment success.

The research assistant reported that he has no access to the CIS. Therefore, he searches in exports from the CIS which are stored in Excel lists. These lists are created for every specific project by a cooperating clinician or nurse.

3.4 IT support - request

The initial, spontaneous answers to the question whether they need IT support for patient recruitment was “No! I can do this in mind and this works well”. Furthermore, most of the participants stated that an IT system would need too much time effort. However, after the interviewees were given time to think about possibilities, the interest and need for electronic support came more and more to mind.

After a while, all participants stated that it would be helpful to have a tool in which some criteria could be entered and which creates a list with patient proposals. This would be great for both study feasibility estimation as well as for patient recruitment. Furthermore, one main concern was to get inter-departmental data access and not only station-specific access. Moreover, all of the interviewees complained that they do not have access to patient data from local doctors with whom they cooperate. One clinician stated that he believes that he needs a very complex system (because of the IC and EC) and, therefore, complex algorithms that cannot be developed. He stated that simple systems can be done by the clinicians and are, therefore, not needed.

Regarding whether self-paced or proactive approaches would be preferred, all interviewees stated that both has advantages and that this depends on the study and the number of possible patients. The main concerns were too many alerts for the proactive solutions, but with a flexible alert time which depends on the study, it would be a well conceivable solution. One interviewee stated that his research needs time critical patients and that it would be absolutely okay to get several alerts a day.

However, all participants stated that electronic support systems have always be kept up-to-date and that this is not always possible in clinical routine. Furthermore, all data would have to become operationalized which is also not always possible. Moreover, most of the interviewees stated concerns with regards data protection.

Another interesting idea that was proposed by one of the clinicians was that he stated that it would be extremely helpful to have a voice recognition software for the creation of doctoral letters. He and the other participants stated that it is very important to keep the data (e.g., main diagnosis) up-to-date, but that does not always happen or takes too long time.

4 Discussion

4.1 Electronic Support for Study feasibility

Overall, the participants reported that most of the feasibility estimation is actually done from memory and that IT support only plays a minor role so far. This seems astonishing because if an up-to-date database of all patients from the last years with the most relevant IC and EC was available, a simple, not time-consuming search would give good estimations [30] [31].

However, one problem that was raised was that often not all EC and IC are known for feasibility estimation, making it challenging to receive acceptable estimations – independent whether there is IT support or not. On the other hand, it was mentioned that there are sometimes too many EC and IC that cannot be remembered accurately. This is one further easy to implement point where electronic support could begin, for example with a defined set of data elements [32].

Furthermore, the interviewees reported that feasibility estimations are not or rather not well documented so far. If an electronic search was performed, this strategy could be saved, making it possible to verify

these steps at later times when needed (e. g., for publications).

4.2 IT Support for Patient recruitment

Just as for feasibility estimations, electronic support plays only a minor role for patient recruitment, today. Again, much is done from memory. However, all interviewees agreed that more data should be stored electronically, and that IT support would indeed be very helpful if there was an up-to-date data base. This is confirmed by several cost-benefit assessments [33] [34].

However, concerns about the possibility of a search for many IC and EC would be possible were raised. There was a need to search for about ten to twenty IC and EC per case and to get a list of patients that fulfill most (but not necessarily all) of them. However, Bache et.al. [35] developed a domain specific query language as an interface between clinicians and stored data to facilitate this task on a technical level and a properly designed software tool has proven to be an enabler for users to correctly create and execute simple feasibility queries with only a relatively small amount of training [36].

All interviewees agreed that the recruitment success depends – beside the complexity of the study – on the clinician and on his personal motivation. This seems to be a further challenge for IT support: Finding IT solutions that motivate the clinic staff to investigate more effort in the recruitment

4.3 Limitations and Future Directions

This study was a first pilot and our results are restricted to one specific German university hospital and cannot be generalized to other institutions. Therefore, the next step should be to repeat this investigation with other hospitals. Because the interviews were very time-consuming and might have affected the clinical routine, an online survey might be a better means for this. Moreover, it seems to be necessary to inform the clinic staff about possibilities of IT support for CT recruitment. Therefore, trainings that are specific for clinical staff should be developed.

5 Conclusions

Although, today, IT is widespread nearly everywhere, it still has a minor standing in the recruitment for CTs. In our study and our specific sample, either feasibility estimations as well as recruitment is mostly done from memory, although there would be many possibilities where IT support could assist. This lack of IT usage and the estimations from memory bind cognitive resources which might district from clinical routine. However, unless IT support, the most relevant factor for successful recruitment is the personal motivation which cannot be changed by IT systems. Overall, we conclude that the recruitment for CT is still a challenge for electronic support and that education of the clinic staff about the possibilities is compellingly necessary.

6 Declarations

6.1 Ethics approval and consent to participate

Written and informed consent was given by all of the participants. Audio recording was additionally approved orally at the beginning of each interview. The study was approved by the local ethics committee of the Friedrich-Alexander University Erlangen-Nuremberg.

6.2 Consent for publication

Not applicable.

6.3 Availability of data and materials

The datasets used and analyzed during the current study cannot be made freely available to preserve anonymity of the participants.

6.4 Competing interests

All authors declare that no competing interests exist.

6.5 Funding

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6.6 Authors' contributions

LB headed the interview design, analyzed the data, wrote the manuscript; TG supported the interview design, contributed to the manuscript; HUP supervised the study design, contributed to the manuscript; AN designed and performed the interviews, analyzed the data, wrote the manuscript. All authors read and approved the final manuscript.

6.7 Acknowledgements

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Abbreviations

CDSS – Clinical Decision Support Systems

CIS – Clinical Information System

CT – Clinical Trial

EC – Exclusion Criteria

EDC – Electronic Data Capture

EDP – Electronic Data Processing

EHR – Electronic Health Record

IC – Inclusion Criteria

IT – Information Technology

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